Check for updates

Narrow Therapeutic Index Drugs: FDA Experience, Views, and Operations

Mark Donnelly[1,*], Lanyan Fang[1], Rajanikanth Madabushi[2], Hao Zhu[3], Markham Luke[4], Crystal Canterbury[5], Bruce Lerman[6], Paramjeet Kaur[7], Devvrat Patel[8], Wanjie Sun[9], Don Schuirmann[9], Steven Dinsmore[10], Mehul Mehta[11,*] and Liang Zhao[1]

The U.S. Food and Drug Administration (FDA) has defined narrow therapeutic index (NTI) drugs as "those drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity." FDA has undertaken efforts to develop NTI assessment criteria and enhance public confidence in generic NTI drugs through public workshops, research, and post-marketing surveillance. In 2015, FDA formed the NTI Drug Working Group to develop a consistent approach to identify NTI drugs and resolve NTI-related scientific and regulatory issues in a transparent and collaborative manner. One key objective of the NTI Drug Working Group is to evaluate potential NTI drugs based on five general characteristics of NTI drugs as highlighted in the case example for theophylline drug products. As of January 5, 2024, there are 33 drug products, with 14 distinct active ingredients, specified as NTI drugs in their respective product-specific guidances (PSGs) for generic drug development. Future collaborative efforts with other agencies to harmonize the terms and definitions for NTI drugs may help enhance clarity and consistency during the drug development and the regulatory review process.

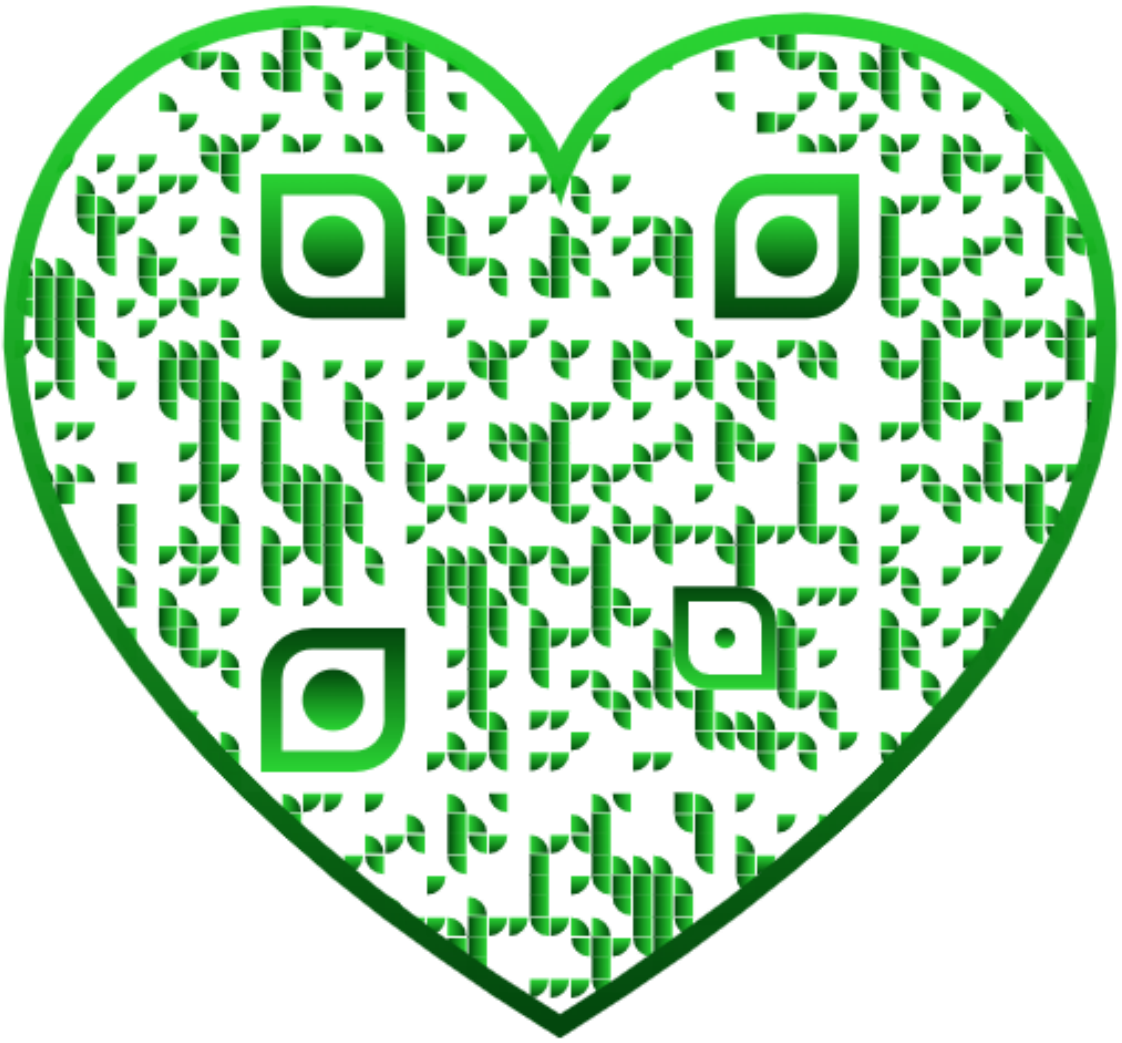
BACKGROUND ON NTI DRUGS

In clinical practice, NTI drugs have generally been considered as drugs which require careful dose titration and routine clinical monitoring for effective therapy.[1–5] NTI drugs are generally used in patient populations for the prophylaxis or treatment of serious illnesses including epilepsy, heart failure, arrythmias, hypothyroidism, thromboembolism, venous thrombosis, asthma, chronic obstructive pulmonary disease, and organ transplantation.[1,5,6,7] Small changes in the dose of NTI drugs may lead to significant changes in pharmacological effects due to the small difference between their effective and toxic concentrations.[1,3,4,5,8] Compared with conventional drugs, NTI drugs pose a higher risk for severe adverse events or lack of efficacy in patients, especially those with advanced age, comorbid conditions, compliance issues, or receiving multiple medications.[1,6,7,9] As a result, clinicians often monitor systemic drug concentration and/or pharmacodynamic (PD) effects in patients administered NTI drugs to safely titrate the dose and provide individualized treatment.[1,5,6,7,9] Historically, the identification of NTI drugs has been empirically based on clinical practice and drugs generally considered as demonstrating an NTI have commonly included warfarin, lithium carbonate, digoxin, phenytoin, theophylline, and tacrolimus.[1,4,5,10,11]

Currently, there is a lack of generally accepted terminology, definition, and standardized quantitative criteria for NTI drugs across regulatory agencies. For example, the Europeans Medicines Agency (EMA), Japan Pharmaceutical Safety Bureau (PSB) (formerly known as the Pharmaceutical and Food Safety Bureau[12]), and Health Canada use the terms "NTI drug," "narrow therapeutic range drug," and "critical dose drug," respectively. Health Canada provides the following definition: "*Critical dose drugs* are defined as those drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life-threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death. Adverse reactions that require significant medical intervention to prevent one of these outcomes are also considered to be serious."[13] EMA does not provide a clear definition or set of criteria to evaluate NTI drugs, but generally recommends a case-by-case NTI assessment based on clinical considerations.[14,15] Japan

[1]Division of Quantitative Methods and Modeling (DQMM), Office of Research and Standards (ORS), Office of Generic Drugs (OGD), Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA), Silver Spring, Maryland, USA; [2]Immediate Office (IO), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS), CDER, FDA, Silver Spring, Maryland, USA; [3]Division of Pharmacometrics (DPM), OCP, OTS, CDER, FDA, Silver Spring, Maryland, USA; [4]Division of Therapeutic Performance (DTP) I, ORS, OGD, CDER, FDA, Silver Spring, Maryland, USA; [5]Division of Legal and Regulatory Support (DLRS), Office of Generic Drug Policy (OGDP), OGD, CDER, FDA, Silver Spring, Maryland, USA; [6]Division of Bioequivalence (DB) I, Office of Bioequivalence (OB), OGD, CDER, FDA, Silver Spring, Maryland, USA; [7]DB II, OB, OGD, CDER, FDA, Silver Spring, Maryland, USA; [8]DB III, OB, OGD, CDER, FDA, Silver Spring, Maryland, USA; [9]Division of Biometrics (DB) VIII, Office of Biostatistics, OTS, CDER, FDA, Silver Spring, Maryland, USA; [10]Division of Neurology (DN) II, Office of Neuroscience (ON), Office of New Drugs (OND), CDER, FDA, Silver Spring, Maryland, USA; [11]Division of Neuropsychiatric Pharmacology (DNP), OCP, OTS, CDER, FDA, Silver Spring, Maryland, USA. *Correspondence: Mark Donnelly (mark.donnelly@fda.hhs.gov) and Mehul Mehta (mehul.mehta@fda.hhs.gov)

Received June 6, 2024; accepted September 18, 2024. doi:10.1002/cpt.3460



PSB provides a list of *narrow therapeutic range drugs* without a definition or specific criteria for inclusion in this list.[16]

The U.S. Code of Federal Regulations (21 CFR 320.33) refers to drugs with a *narrow therapeutic ratio* with the following definition: (1) There is less than a 2-fold difference in median lethal dose (LD50) and median effective dose (ED50) values -or- there is less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood; and (2) Safe and effective use of the drug products requires careful titration and patient monitoring.[17] However, certain challenges have been noted with the practicality of this definition and its use in clinical and regulatory settings.[4,10] In 1995, FDA published general guidance for industry which provided a list of *narrow therapeutic range* drugs, but definitions and criteria for this list were not provided.[18] In 1999, FDA first published draft guidance (since revised) defining *narrow therapeutic range* drug products as "those containing drug substances that are subject to therapeutic drug monitoring, and/or where product labeling specifies that the drug is a narrow therapeutic range drug."[19] Subsequently, FDA published draft guidance in 2006[20] and 2012[21] (since revised and incorporated into other guidance), listing cytochrome P-450 (CYP) substrates with a *narrow therapeutic range*. CYP substrates with a narrow therapeutic range refers to drugs whose exposure–response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns. In 2010 and 2011, FDA held advisory committee meetings to discuss, among other topics, the terms and definitions used to describe these types of drugs.[22,23] Consistent with the advisory committee recommendations, FDA is currently using the term *NTI drug*, defined as "those drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity."[4,5,10,24,25] In light of the historically inconsistent use of these terms, collaborative efforts to harmonize the terms and definitions for NTI drugs across regulatory agencies may help enhance clarity and consistency during the drug development and the regulatory review process.

GENERIC NTI DRUGS

Considering the high cost of medicines and evidence linking greater generic competition with lower drug prices, states in the U.S. have adopted laws and/or regulations that encourage the substitution of innovator drug products with generics and FDA's Drug Competition Action Plan has been implemented to further encourage market competition for generic drugs and to bring greater efficiency and transparency to the generic drug review process.[26–29] Regardless of the characteristics of a drug (i.e., NTI or not), innovator drug products may be substituted with approved generic drug products that are designated to be therapeutically equivalent with the full expectation that the substituted product can be expected to have the same clinical effect and safety profile as the prescribed product when administered to patients under the conditions specified in the labeling.[28,30] It is important to note that therapeutic equivalence evaluations are considered a scientific judgment based upon evidence, while generic substitution may involve economic, policy, or legal factors.[28] To establish therapeutic equivalence, a generic drug product must be: (1) a pharmaceutical equivalent (2) for which bioequivalence has been demonstrated, and (3) that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[28,30] Pharmaceutical equivalence ensures that drug products: (1) contain identical amounts of the identical active drug ingredient in the identical dosage form and route of administration, and (2) meet identical compendial or other applicable standards of identity, strength, quality, and purity.[28,30] Bioequivalence (BE) is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents (or pharmaceutical alternatives) becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.[28,30] BE ensures that drug products: (1) do not present a known or potential BE problem, and they meet an acceptable *in vitro* standard, or (2) if they do present such a known or potential problem, they are shown to meet an appropriate BE standard.[28] FDA publishes *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the *Orange Book*, which identifies approved drug products, patent and exclusivity information, and therapeutic equivalence codes, among other information.[28] Also, FDA publishes draft and final product-specific guidances (collectively, PSGs) to share its current thinking and recommendations on the most appropriate methodology to establish therapeutic equivalence between innovator drug products and generics.[31] Consequently, FDA facilitates generic drug development of NTI drugs through PSG publications and revisions.[31,32] In addition, FDA has published recommendations in guidance for industry that are unique to NTI drugs or drugs with certain NTI drug characteristics (**Table 1**).

BE ASSESSMENT OF CONVENTIONAL DRUGS

For most drug products, the focus of BE studies is on the release of the drug substance from the drug product into the systemic circulation.[25] During such BE studies, an applicant compares the systemic exposure profile of a test drug product (generic) to that of the reference standard (RS), also referred to more generally as the reference product.[25,28] The RS is the drug product selected by FDA that an applicant seeking approval of an abbreviated new drug application (ANDA) must use in conducting an *in vivo* BE study required for approval.[28] Ordinarily, FDA will select the reference listed drug (RLD) designated in the *Orange Book* as the RS.[28,30] However, the RS and RLD may be different in some circumstances, such as when the RLD has been withdrawn from sale for reasons other than safety or effectiveness.[28] BE studies frequently rely on pharmacokinetic (PK) end points, such as peak concentration (C_{max}) and the area under the curve (AUC), in an accessible biological matrix (e.g., whole blood, plasma, and/or serum) to evaluate the rate and extent of absorption, respectively.[25] For most dosage forms that release a drug intended to be systemically available, FDA recommends that applicants conduct BE studies using a single-dose, two-period, two-sequence, two-treatment (i.e., two-way crossover) design with healthy subjects or other populations, as appropriate.[25] In this design, subjects are administered the test product (T) and reference product (R) in

15326535, 2025, 1, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3460 by Us Fda, Wiley Online Library on [13/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1 FDA guidance for industry with specific recommendations for NTI drugs

FDA guidance for industry	Topic
Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an ANDA (August 2021, draft)[25]	Recommended study design and statistical analysis for BE assessment of NTI drugs
Statistical approaches to establishing bioequivalence (December 2022, draft)[33]	Method for statistical analysis using the reference-scaled average BE approach for NTI drugs
M9 biopharmaceutics classification system-based biowaivers (May 2021)[55]	NTI drugs are excluded from consideration for a BCS-based biowaiver
Dissolution testing and acceptance criteria for immediate-release solid oral dosage form drug products containing high solubility drug substances (August 2018)[38]	NTI drugs are excluded from this guidance because of the critical relationship between the bioavailable dose and clinical performance
SUPAC-IR: Immediate-release solid oral dosage forms: scale-up and post-approval changes: chemistry, manufacturing and controls, *in vitro* dissolution testing, and in vivo bioequivalence documentation (November 1995)[18]	Tests and filing documentation for post-approval changes to drugs with a narrow therapeutic range[a]

BE, bioequivalence; BCS, biopharmaceutics classification system; NTI, narrow therapeutic index. [a]The list of narrow therapeutic range drugs provided in this guidance was published prior to the establishment of the terminology and definition of NTI drugs currently used by FDA.

separate periods using a T-R or R-T sequence.[25] For the statistical analysis, average PK values for the T and R products are compared using the two one-sided tests (TOST) procedure.[25,33] This method is commonly referred to as average BE analysis or unscaled average BE analysis. The primary comparison is the ratio, rather than the difference, between average PK parameter data from the T and R formulations.[33] Since the statistical analysis method recommends using logarithmic transformation of the PK data, it allows for inferences about the difference between the two means on the log scale, which can then be retransformed into inferences about the ratio of the two averages (geometric means) on the original scale.[33] For average BE analysis of conventional drugs (i.e., not highly variable drugs or NTI drugs), the 90% confidence interval (CI) of the geometric mean ratio (GMR) for each PK parameter should fall entirely within 80.00% and 125.00% to meet BE acceptance criteria.[25,33]

REGULATORY CONSIDERATIONS FOR BE ASSESSMENT OF NTI DRUGS

When compared with conventional drugs, FDA recommends tighter quality and BE standards to ensure the therapeutic equivalence of NTI drugs to the RLD.[4,34,35] The tighter BE standards for NTI drugs are based in large part on recommendations from previous advisory committee meetings,[22,23] research using modeling and simulation approaches to investigate potential BE approaches and acceptance criteria for NTI drugs,[4,11] and internal discussions at FDA. The BE approach and acceptance criteria used for generic drugs are generally the same as those used in BE studies for innovator drug products.[10,36] BE studies with the innovator drug product may be conducted to support changes in the pivotal clinical trial formulation and the to-be-marketed drug formulation or to support certain post-approval changes in manufacturing, inactive ingredients, or dosage form.[10,36] Due to the complexities associated with NTI drugs, new drug application (NDA) applicants are recommended to contact the appropriate review division at FDA for additional information.[36]

For BE assessment of NTI drugs, FDA recommends *in vivo* BE studies using the reference-scaled average BE approach with a four-way, fully replicated crossover study design that permits the simultaneous equivalence comparison of the mean and within-subject variability (WSV) of the T product and R product (i.e., reference standard).[4,25,32,33] In a four-way, fully replicated crossover study design, the T and R products are administered to subjects twice over four periods using a T-R-T-R or R-T-R-T sequence. Administration of the T product and R product twice permits the calculation of the within-subject standard deviation of the test product (s_{WT}) and reference standard (s_{WR}), respectively, which is required for the WSV comparison between the T product and R product. This WSV comparison is believed to be critical to address concerns that increased variability in drug concentration of the T product may increase the likelihood of therapeutic failures and/or serious adverse events.[4,24] In addition to the WSV comparison, the BE assessment of NTI drugs uses tighter BE limits compared with conventional drugs. Since most NTI drugs demonstrate low-to-moderate WSV (i.e., ≤30%) in their PK parameters, an important feature for accurate dose adjustment and prediction of clinical response, the BE limits for NTI drugs are tightened based on s_{WR} with a cap at the conventional BE limits of 80.00%–125.00%.[4,24] One common misconception is that the current FDA BE approach for NTI drugs uses tightened BE limits fixed at 90.00–111.11%.[6,37] For FDA, the BE limits for NTI drugs are 90.00–111.11% only when s_{WR} is 0.1. When s_{WR} is not 0.1, these BE limits are scaled based on s_{WR} using a regulatory constant (σ_{W0}) of 0.10.[4,24] Thus, the implied BE limits may be narrower than 90.00% to 111.11% when s_{WR} is <0.1, or wider than 90.00% to 111.11% when s_{WR} is >0.1, but the conventional BE limits of 80.00%–125.00% may never be exceeded.[4,24] **Figure 1** shows the scaled BE limits for NTI drugs and provides an example of hypothetical BE results of single PK parameter for an NTI drug at two different s_{WR} values. In this example, the hypothetical BE results for an NTI drug with GMR of 0.95 and 90% CI of 0.88–1.02 meet the scaled BE limits of approximately 0.85–1.17 at s_{WR} of 15%. However, the same BE results fail to meet the scaled BE limits of approximately 0.90–1.11 when the reference product exhibits a lower s_{WR} of 10%. General FDA draft guidance[25,33] and PSGs[31,32] recommend that *in vivo* BE studies for NTI drugs should pass the following criteria for each PK parameter: (1) 95% upper confidence bound (defined in FDA guidance[25,32]) is less than or equal to zero using the reference-scaled

15326535, 2025, 1, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3460 by Us Fda, Wiley Online Library on [13/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

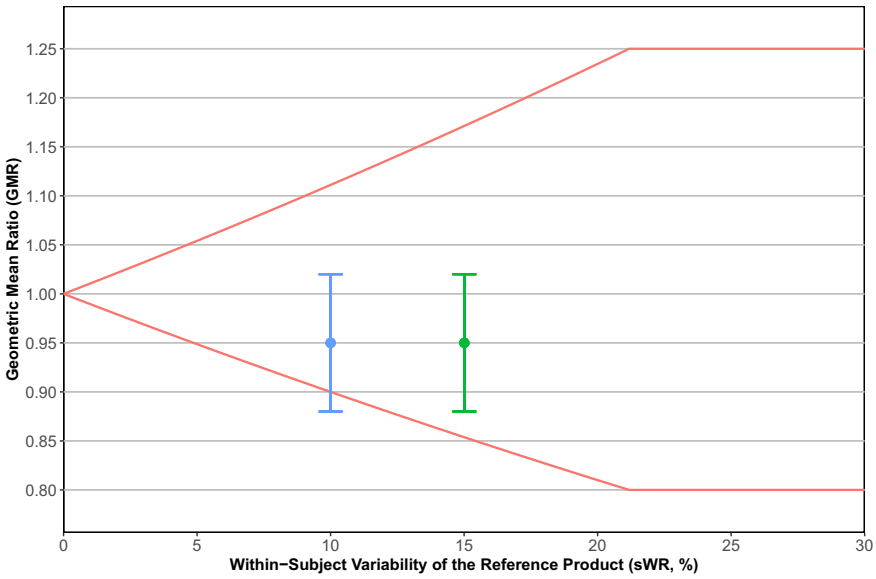


Figure 1 Scaled bioequivalence (BE) limits for NTI drugs. BE limits for NTI drugs are scaled based on within-subject variability of the reference product (s_{WR}) and capped at the conventional BE limits of 80.00%–125.00% when s_{WR} is approximately 21% or greater (solid red line). Hypothetical BE results of a single PK parameter for an NTI drug a with geometric mean ratio (GMR) of 0.95 and 90% confidence interval (CI) of 0.88–1.02 at s_{WR} of 10% and 15% are shown in blue and green, respectively. The BE results meet the scaled BE limits of approximately 0.85–1.17 at s_{WR} of 15% (green). However, the same BE results fail to meet the scaled BE limits of approximately 0.90–1.11 at a lower s_{WR} of 10% (blue).

average BE analysis, (2) 90% CI of the GMR is within 80.00% and 125.00% using the unscaled average BE analysis, and (3) the upper limit of the 90% equal-tails CI for σ_{WT}/σ_{WR} is ≤2.500. In addition to the recommendation for conducting the *in vivo* BE studies described above, the PSGs for NTI drugs may also recommend conducting *in vitro* BE studies such as dissolution testing, or providing other BE criteria such as information related to a waiver request of *in vivo* testing.[32] When finalized, FDA's general guidances and PSGs recommending BE approaches for NTI drugs will represent FDA's current thinking and expectations on how to develop a generic NTI drug product that is bioequivalent to the RLD.[25,32]

It is important to note that ANDAs filed but not yet approved may be impacted by decisions regarding the NTI characteristics of a drug. Following the decision that a drug product meets the general characteristics of an NTI drug, FDA will update the PSG to recommend demonstrating BE using the BE approach for NTI drugs, including the four-way, fully replicated study design and BE criteria for NTI drugs.[25,32] Where an applicant (or prospective applicant) has already commenced an *in vivo* BE study before a new or revised PSG recommends the 4-way, fully replicated study design and BE criteria for NTI drugs, the applicant (or prospective applicant) may request a PSG teleconference, pre-submission PSG meeting, and/or post-submission PSG meeting to obtain Agency feedback on how the new or revised PSG may potentially impact their development program.[39]

In some situations, ANDAs are approved prior to FDA's determination that the drug is considered an NTI drug and therefore without using a four-way, fully replicated study design and BE criteria for NTI drugs. In general, FDA determines that a drug product is BE and therapeutically equivalent to the RLD at the time of its approval.[24] Although FDA considers its current BE approach for NTI drugs approach the most accurate, sensitive, and reproducible approach for demonstrating BE[40], FDA's current recommendations do not establish that prior-conducted BE studies could not detect clinically significant differences in the PK profiles of the generic product and the RLD[41]. FDA generally does not expect application holders of approved ANDAs to re-demonstrate BE according to the BE recommendations revised after approval of that ANDA, unless the Agency becomes aware of evidence indicating that the ANDA product(s) may not be therapeutically equivalent to the respective RLD or an application-holder proposes to make a change to the approved drug product(s) that necessitates new BE studies to support approval of the change.[24,41,42]

FDA RESEARCH INITIATIVES FOCUSED ON NTI DRUGS

FDA has developed several initiatives and research efforts to ensure the quality of NTI drugs, verify therapeutic equivalence between innovator and generic NTI drugs, improve patient perceptions about generic NTI drugs, and identify any potential bias in reporting safety and efficacy issues related to NTI drugs.[34,35,43–48] At the pre-market stage, FDA efforts have been focused on methods for identifying NTI drugs and ensuring risk-based BE and product quality standards using innovative modeling and simulation approaches.[34,35,43] At the post-market stage, FDA performs active and passive surveillance efforts, using FDA's Adverse Event Report System (or FAERS)[49] and Sentinel,[50] to ensure the safety of NTI drugs.[34,35] Likewise, FDA monitors reports related to the therapeutic equivalence of generic NTI drugs from patients, industry, and healthcare providers to identify and resolve potential quality or BE concerns.[46–48] Moreover, FDA has funded contracts and grants to experts in academic institutions and contract research organizations for research focused on generic NTI drug

15326535, 2025, 1, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3460 by Us Fda, Wiley Online Library on [13/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

substitution, including BE studies in patients with monitoring of adherence, efficacy, and safety.[24,43–45] Key findings from research on generic NTI drugs are usually published in literature and/or FDA's Generic Drug User Fee Amendments (GDUFA) Science and Research Reports.[51] Furthermore, FDA is also evaluating the performance of current and proposed BE assessment criteria for NTI drugs to enhance harmonization across regulatory agencies.

NTI DRUG WORKING GROUP AT FDA

Based on the needs to coordinate NTI-related activities and to promote regulatory consistency within the Agency, FDA conducted cross-office scientific discussions regarding NTI drug issues across the Center for Drug Evaluation and Research (CDER). In 2015, FDA formed the NTI Drug Working Group to develop a consistent approach to identify NTI drugs and resolve NTI-related scientific and regulatory issues in a transparent and collaborative manner. A few key objectives of the NTI Drug Working Group are to: (1) Identify new NTI products based on information from drug application reviews, scientific literature, and expert opinion; (2) Develop a consistent process for monitoring and re-evaluating NTI drugs in the early post-marketing stage to support timely availability of PSG recommendations for generic drug development; (3) Evaluate research and tools that could aid NTI classification such as exposure–response modeling, or clinical usage data analysis; and (4) Maintain a repository of institutional knowledge related to identification and evaluation of the therapeutic index of drug products and provide scientific and regulatory consultation to CDER review divisions.

The CDER organizations currently represented at the NTI Drug Working Group are summarized in **Table 2**. Co-chair positions, designated from the Office of Research and Standards (ORS) and Office of Clinical Pharmacology (OCP), are responsible for directing the activities of the NTI Drug Working Group and reporting back to the CDER Lifecycle Management Board periodically on progress, accomplishments, and priorities. The core membership comprises but is not limited to, representatives from ORS, including the Division of Quantitative Methods and Modeling (DQMM) and the Division of Therapeutic Performance (DTPI, DTPII); Office of Translational Sciences (OTS), including OCP and Office of Biostatistics (OTS/OB); Office of New Drugs (OND); Office of Bioequivalence (OGD/OB); and Office of Generic Drug Policy (OGDP). Core members are nominated by the corresponding office directors for a 3-year term. Representatives from other offices and divisions, such as the Office of Pharmaceutical Quality (OPQ) and Office of Surveillance and Epidemiology (OSE) are invited as needed, given the topics to be discussed. The agenda topics for the NTI Drug Working Group meeting are prioritized based on various factors including regulatory commitments and potential impact. A typical meeting consists of a stakeholder case presentation on an NTI drug-related topic, such as a preliminary NTI assessment of a drug product, followed by solicitation of feedback from subject matter experts and an open discussion with all members. The co-Chairs facilitate the meeting discussion and decision-making process, but decisions are reached by consensus. If a clear consensus cannot be reached, there is a voting process to determine the final decisions and action items.

Table 2 FDA NTI drug working group membership and organization

CDER organization
Office of Generic Drugs (OGD)

• Office of Research and Standards (ORS)[a]
  • Division of Quantitative Methods and Modeling (DQMM)
  • Division of Therapeutic Performance I (DTPI)
  • Division of Therapeutic Performance II (DTPII)
• Office of Bioequivalence (OGD/OB)
• Office of Generic Drug Policy (OGDP)

Office of Translational Sciences (OTS)
• Office of Clinical Pharmacology (OCP)[a] • Office of Biostatistics (OTS/OB)
Office of New Drugs (OND)
Office of Surveillance and Epidemiology (OSE)
Office of Pharmaceutical Quality (OPQ)

[a]A representative from ORS and OCP serve as co-Chairs for the NTI Drug Working Group.

TRIGGERS FOR NTI DRUG ASSESSMENT

There are numerous instances which may necessitate an NTI assessment of a drug at the NTI Drug Working Group. Various terms such as narrow therapeutic range, NTI, and narrow therapeutic ratio have been used inconsistently in the drug application review process, approved product labeling, published literature, and regulatory guidance. The NTI Drug Working Group strives to harmonize and clarify the use of these terms within FDA and internationally. The NTI Drug Working Group may also consider the NTI status of a drug in response to inquiries or submissions from the pharmaceutical industry. For example, based on use of NTI-related terminology in product labeling or publicly available NDA reviews, drug applicants have sought feedback from FDA on considerations of certain products as NTI drugs to guide their planned BE study design and assessment criteria, especially in situations where a PSG has not been published. Also, applicants have submitted controlled correspondence related to Biopharmaceutics Classification System (BCS)-based biowaivers, which do not apply to NTI drugs.[55] Similarly, the NTI Drug Working Group may review or provide additional information on the NTI status of a drug in response to a citizen petition to FDA.[37,52,53] NTI assessments may also need to be completed to support regulatory review of an ANDA or address specific questions proposed to FDA in product development meetings.

Another common trigger for an NTI assessment is the development or revision of BE recommendations in PSGs for generic drug development.[31] To illustrate, during the development of a new draft PSG for clonazepam oral tablets, it was observed that this drug product was described as a narrow therapeutic range drug by another regulatory agency.[16] Following an assessment at FDA, the NTI Drug Working Group determined that this drug product did not possess the general characteristics of an NTI drug, and thus the BE approach for NTI drugs was not recommended in the PSG.[56] NTI assessments may also be triggered to support harmonization efforts across regulatory agencies. FDA is a Founding Regulatory Member of The International Council for Harmonization of

15326535, 2025, 1, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3460 by Us Fda, Wiley Online Library on [13/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Technical Requirements for Pharmaceuticals for Human Use (ICH) and is participating in efforts to provide greater regulatory harmonization worldwide.[57] Benefits of regulatory harmonization related to generic drug development of NTI drugs may potentially include consistent NTI terminology and definitions, consistent BE study design and assessment criteria, and improved safety, quality, and availability of generic NTI drugs, to name a few. Recently, ICH published Guideline M13A, which is the first guideline in a series intended to provide recommendations on conducting BE studies during both the development and post-approval phases for immediate-release (IR) solid oral dosage forms.[57] ICH is planning to publish a third guideline in the series, M13C, which will cover data analysis and BE assessment for NTI drugs and other topics.[57] It is hopeful that these efforts will address the regulatory impact of inconsistent use of NTI drug terminology and improve the harmonization of BE assessment methods for NTI drugs.

In summary, the assessment of candidate drug products for consideration as NTI drugs may be driven by various factors including, but not limited to, the inconsistent use of NTI drug terminology, inquiries from the pharmaceutical industry, regulatory reviews, product development meetings, guidance development, and FDA and international harmonization efforts.

NTI ASSESSMENT METHODS AND IMPACT

The NTI Drug Working Group evaluates potential NTI drugs based on five general characteristics of NTI drugs previously described in the literature.[4] Data sources used for NTI assessments vary greatly including drug product labeling, drug applications, literature data, clinical practice data, monitoring of safety and efficacy data (e.g., FAERS[49] and Sentinel[50]), exposure–response modeling, and/or other sources. FDA's decision to consider a drug product as an NTI drug may have a significant regulatory impact on BE and quality standards, guidance revisions, regulatory review of pending ANDAs, post-marketing surveillance, research on generic substitution, and manufacturing site inspections. **Figure 2** provides a high-level summary of the NTI drug evaluation process including NTI assessment triggers, data sources, assessment criteria, and regulatory impact at FDA. **Table 3** provides a high-level summary of NTI drug characteristics,[4] NTI drug assessment challenges, and a case example of an NTI drug assessment for theophylline drug products. Theophylline has been approved by FDA in various dosage forms (some of which are currently discontinued), including an injectable dosage form, oral elixir, oral solution (elixir), oral solution, oral suspension, oral syrup, oral tablet, oral chewable tablet, oral ER tablet, oral capsule, and oral ER capsule. Based on the information reviewed, FDA has concluded that theophylline is considered an NTI drug and accordingly published three revised draft PSGs.[58–60]

FDA LIST OF NTI DRUGS

One of the primary objectives of this manuscript is to communicate key findings for NTI assessments at the NTI Drug Working Group. **Table 4** lists drug products demonstrating NTI drug characteristics with published PSGs. As of January 5, 2024, there are 33 drug products, with 14 distinct active ingredients, considered NTI drugs in their respective PSGs. Candidate drug products considered as "not NTI," based on a failure to meet the characteristics of an NTI drug, or "undetermined," due to lack of sufficient information for a complete NTI assessment, are not reported in **Table 4**. If a drug product meets the characteristics of an NTI drug, it is typically communicated to the public through revisions to the PSGs for generic drug development. It is important to note that the list in **Table 4** is subject to revision by FDA based on, among other factors, additional data and information, revision of NTI assessments, performance of new NTI assessments, PSG revisions, and publication of new PSGs.

There are a few special considerations that should be noted with regard to the assessments and list of NTI drugs in **Table 4**. First, it is important to clarify that consideration of a drug product as an NTI drug is not based solely on the active ingredient. For example, cyclosporine oral capsules are considered as NTI drugs in their respective PSGs,[61,62] while ophthalmic drug products containing cyclosporine fail to meet the characteristics of NTI drugs, and thus are not considered as NTI drugs.[63–65] Second, oncology drug products are generally not included in the list of drug products that demonstrate NTI drug characteristics because treatment is commonly titrated based on safety and/or tolerability and more severe adverse reactions may be tolerated in these patients. To illustrate, everolimus oral tablet and everolimus tablet for oral suspension, approved under NDA 022334 and NDA 203985, respectively, are

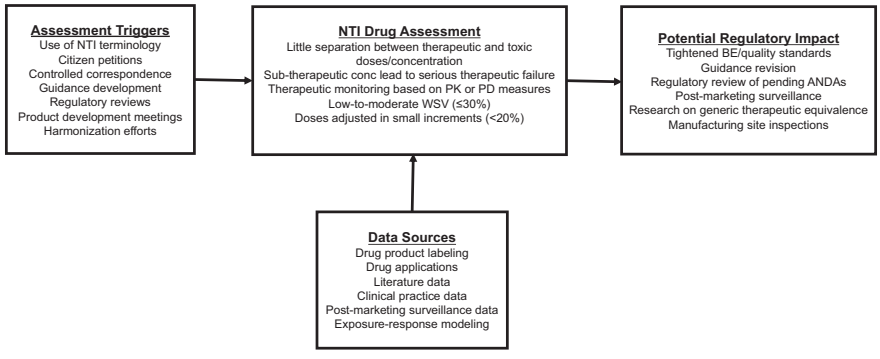


Figure 2 Summary of the NTI drug assessment process and potential regulatory impact at FDA. ANDA, abbreviated new drug application; conc, concentration; FDA, the U.S. Food and Drug Administration; NTI, narrow therapeutic index; PK, pharmacokinetic; PD, pharmacodynamic; WSV, within-subject variability.

15326535, 2025, 1, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3460 by Us Fda, Wiley Online Library on [13/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 3 Summary of NTI drug characteristics, NTI drug assessment challenges and observations, and case example of the NTI drug assessment for theophylline drug products

NTI drug characteristics[4]	NTI drug assessment challenges and observations	Case example: NTI drug assessment for theophylline drug products
Little separation between therapeutic and toxic doses/ concentrations	• There may be insufficient clinical data to support dose–response relationships and adequately quantify the separation between effective and toxic doses. For instance, the median lethal dose and median effective dose are commonly not available.[4,5] • Dose–response relationships for efficacy and safety should be considered at both the population and individual levels which adds complexity to the assessment. • The assessment should consider confounding factors related to the patient population(s). For instance, the therapeutic index of a patient may change following treatment, due to the development of tolerance or sensitization,[8] or may vary among certain subpopulations. • Challenges exist with the development of a harmonized approach across various drug classes and indications due to differences in the classification and reporting of adverse events in safety data.	There is little separation between therapeutic and toxic concentrations of theophylline. The target therapeutic serum concentration for theophylline is considered to be 10–20 mcg/mL.[80–83] Although bronchodilation occurs over the serum theophylline concentration range of 5–20 mcg/mL, clinically important improvement in symptom control has been found in most studies when peak serum theophylline concentrations is >10 mcg/mL.[81,83–87] Adverse events have been reported at serum concentrations above 15 mcg/mL, but these were mild, typically of gastrointestinal nature and tolerable.[83,88–90] However, at serum concentrations that exceeded 20 mcg/mL, toxicity manifestations were life-threatening and included, but were not limited to arrhythmias and seizures.[91–95] Also, an internal review of post-marketing safety data revealed that serious adverse events were observed in patients with serum theophylline concentrations near or above 20 mcg/mL. Thus, the ratio of the minimum toxic concentration (20 mcg/mL) to the minimum effective concentration (10 mcg/mL) for serum theophylline is 2, which has been decided to meet the criteria for little separation between therapeutic and toxic drug concentrations.
Sub-therapeutic concentrations lead to serious therapeutic failure	• The assessment may need to consider not only the impact, but also the likelihood of reaching sub-therapeutic concentrations due to inadequate dose adjustment, drug–drug interactions, disease states, food effects on absorption, genetic polymorphisms, and other factors. • The assessment should consider numerous factors including the patient population, drug product indication, clinical risk, and disease progression, which presents challenges for a harmonized approach. • There may be a lack of a clear and consistent definition for serious therapeutic failure across various drug classes and indications.	Sub-therapeutic serum theophylline concentrations are associated with asthmatic and pulmonary events typically requiring hospitalization. For instance, sub-therapeutic serum theophylline concentrations of <10 mcg/mL were associated with dyspnea and shortness of breath in chronic obstructive pulmonary disease (COPD) and asthma patients with potentially fatal outcomes.[80,81,85] Also, dose adjustments may be needed due to interactions with theophylline and many other drugs.[80]
Therapeutic monitoring based on PK or PD measures	• Therapeutic monitoring may be performed occasionally, such as during the treatment initiation period, instead of routine, or only in a special population. • Therapeutic monitoring may be performed not only for NTI drugs but also for some conventional drugs due to potential patient compliance problems or other reasons. • The degree to which the therapeutic monitoring mitigates the risk of serious adverse events or lack of efficacy is often not well studied.	Patients treated with theophylline undergo therapeutic monitoring based on PK measures. There is no clearly established relationship between dose and serum concentration, possibly due to the significant variability in the systemic drug clearance of theophylline observed in healthy volunteers as well as in patients with complicated health conditions.[80,83,90] However, there is a direct relationship between serum concentrations and efficacy[81,87,88] or drug-related toxicity[84,89,90]. It has been reported that PK-guided dosing of theophylline, which targeted the serum concentration therapeutic range of 10–20 mcg/mL, resulted in fewer drug-related toxicity events.[89,96] Since the separation between therapeutic and toxic serum concentrations is narrow, the dose of theophylline must be individualized on the basis of peak serum theophylline concentration measurements in order to achieve a dose that will provide maximum potential benefit with minimal risk of adverse effects.[80,89]

(Continued)

15326535, 2025, 1, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3460 by Us Fda, Wiley Online Library on [13/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 3 (Continued)

NTI drug characteristics[4]	NTI drug assessment challenges and observations	Case example: NTI drug assessment for theophylline drug products
Low-to-moderate WSV (≤30%)	• For older drug products, it may be time-consuming, yet necessary, to collect data which are not electronically available. • The assessment may include an evaluation of various dosage forms containing the same active ingredient and a large number of *in vivo* BE studies, which may be time-consuming and challenging. • There may be a lack of data available from BE studies conducted using a four-way, fully replicated crossover design, which allows for the direct estimation of s_{WR}. *In vivo* BE studies conducted using a two-way crossover design permit the assessment of residual variability, often reported as RMSE or ISCV, which includes WSV for test and reference drug products as well as the subject-by-formulation interaction variance.[4]	Consistent with previous BE recommendations for theophylline drug products, *in vivo* BE studies were historically conducted using a single-dose, two-way, crossover design. Yu *et al*. reviewed the results of three *in vivo* BE studies using a single-dose, two-way, crossover design, in ANDAs for theophylline drug products and reported mean RMSE of 17.9% (12.8–24.2) and 18.2% (11.8–24.8) for AUC_{0-t} and C_{max}, respectively.[4] Based on these results and other unpublished data from BE studies using the four-way, fully replicated crossover design, theophylline appears to demonstrate low-to-moderate WSV (≤30%).
Doses adjusted in small increments (<20%)	• The percentage dose adjustment may change across the various recommended dosing regimens with larger adjustments generally occurring at the lower doses. Also, the percentage dose adjustment is generally different for ascending and descending dose adjustments. These factors add complexity to the assessment. • Tablet scoring may present confusion on whether dose adjustments are made by splitting the tablet if it is not clearly described in the product labeling.	Theophylline doses are adjusted in small increments in the clinic. Theophylline dosing recommendations for individual patients must take into account the unique clinical characteristics of each patient and recommendations in the product labeling serve as the upper limit for dosage adjustments.[80] Dose adjustments are recommended in patients receiving theophylline with serum concentrations falling outside the therapeutic concentration range of 10–20 mcg/mL. Theophylline dose adjustments in clinical practice generally range between 10% and 25% of the current dose.[80]

AUC_{0-t}, area under the concentration-time curve (0-t); ANDA, abbreviated new drug application; BE, bioequivalence; C_{max}, maximum concentration; ISCV, intra-subject coefficient of variation; NTI, narrow therapeutic index; PK, pharmacokinetic; PD, pharmacodynamic; RMSE, root mean squared error; WSV, within-subject variability.

kinase inhibitors with indications in cancer treatment,[66] and published PSGs for generic drug development do not state that these products are considered as NTI drugs.[67,68] Conversely, everolimus oral tablet, approved under NDA 021560, is an mTOR immunosuppressant indicated for the prophylaxis of organ rejection in adult patients,[69] and its current draft PSG notes that this drug product is considered an NTI drug.[70] Third, some drug products may not be considered as NTI drugs, but their PSGs may specify special BE recommendations based on the findings of NTI assessment. For instance, the PSGs for several novel oral anticoagulants, including dabigatran etexilate mesylate oral capsules,[71] rivaroxaban oral tablets,[72] and edoxaban tosylate oral tablets,[73] specify that these products demonstrated steep exposure–response relationships for efficacy and/or safety. However, these drug products fail to meet the characteristics of NTI drugs and may even demonstrate high WSV (>30%) in PK parameters. But, in these cases, the reference-scaled average BE approach for highly variable drugs, which allows for widening the BE limit based on s_{WR},[25] is not recommended due to concerns with the steep exposure–response relationships for efficacy and/or safety. Instead, PSGs for these drug products recommend a four-way, fully replicated crossover design for the *in vivo* BE studies with BE criteria based on unscaled average BE limits of 80.00%–125.00% and a WSV comparison between test product and RS. These examples, and other factors not described here, illustrate the complexity of NTI drug assessments and may help explain differences in BE recommendations for drug products with the same active ingredient.

COMPARISON WITH OTHER REGULATORY AGENCIES

Many regulatory agencies report NTI drugs based on the active ingredient instead of the drug product. **Table 5** shows a comparison of active ingredients (or drug products containing certain active ingredients) referred to as NTI drugs or related terminology across a few regulatory agencies. The authors could not find an EMA repository for an NTI drug list, so published PSGs were reviewed for descriptions of drugs as "NTI" or related term.[15] The authors identified five drugs (acenocoumarol,[74] colchicine,[75] everolimus,[76] sirolimus,[77] and tacrolimus[78]) described as NTI drugs and one drug (levothyroxine[79]) described as a critical dose drug by EMA. Consistent with FDA, EMA refers to sirolimus and tacrolimus as NTI drugs, and everolimus is considered an NTI drug in the transplant setting. However, there are inconsistencies between EMA and FDA when comparing other drugs, including the terms used to describe levothyroxine. All of the drugs considered as "critical dose drugs" by Health Canada[13] are considered NTI drugs by FDA with the exception of flecainide. Japan PSB provides an extensive list of drugs considered "narrow therapeutic range drugs" including an entire class of compounds

15326535, 2025, 1, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3460 by Us Fda, Wiley Online Library on [13/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 4 Drug products demonstrating NTI drug characteristics with published PSGs

Active ingredient	Administration route/dosage form	RLD/RS Application No.	Last PSG publication date
Carbamazepine	Oral tablet	016608	September 2015[a]
	Oral tablet, ER	020234	March 2015[a]
	Oral capsule, ER	020712; 021710	March 2015[a]
	Oral suspension	018927	March 2015[a]
	Oral tablet, chewable	018281	August 2022[a]
Cyclosporine	Oral capsule	050625	April 2016[a]
	Oral capsule	050715	April 2016[a]
Digoxin	Oral tablet	020405	August 2017[a]
Divalproex sodium	Oral tablet, DR	018723	December 2016[a]
	Oral capsule, DR Pellets	019680	December 2016[a]
	Oral tablet, ER	021168	December 2016[a]
Everolimus	Oral tablet	021560	June 2020[a]
Levothyroxine sodium	Oral tablet	021116; 021210; 021301; 021342; 021402	December 2014[a]
	Oral capsule	021924	November 2018[a]
Liothyronine sodium	Oral tablet	010379	February 2022[a]
Lithium carbonate	Oral tablet, ER	076691	May 2023[a]
	Oral tablet, ER	018027	May 2023[a]
	Oral tablet	018558	May 2023[a]
	Oral capsule	017812	May 2023[a]
Phenytoin/Phenytoin sodium	Oral tablet, chewable	084427	May 2017[a]
	Oral suspension	008762	May 2017[a]
	Oral capsule, ER	040298	December 2014[a]
	Oral capsule, ER	084349	December 2014[a]
Sirolimus	Oral tablet	021110	September 2015[a]
Tacrolimus	Oral tablet, ER	206406	June 2016[a]
	Oral capsule, ER	204096	July 2014[a]
	Oral capsule	050708	December 2012[a]
	Oral for suspension	210115	August 2022[a]
Theophylline	Oral tablet, ER	040560	August 2020[a]
	Oral capsule, ER	081034	August 2020[a]
	Oral tablet, ER	090430; 086998; 085328	May 2022[a]
Valproic acid	Oral capsule	018081	August 2017[b]
Warfarin sodium	Oral tablet	009218	December 2012[a]

PSG, product-specific guidance; RLD, reference listed drug; RS, reference standard; No., number; ER, extended-release; DR, delayed-release. [a]Draft PSG. [b]Finalized PSG.

such as sulfonylurea antidiabetic drugs (acetohexamide, glibenclamide, gliclazide, glyclopyramide, tolazamide, and tolbutamide) and theophylline compounds (aminophylline, choline theophylline, diprophylline, proxyphylline, and theophylline).[16] The list of narrow therapeutic range drugs by Japan PSB is more exhaustive than the list of NTI drugs provided by FDA, possibly due to the different definitions and assessment criteria used to evaluate these drugs. Most of the drugs considered NTI drugs by FDA are listed as narrow therapeutic range drugs by Japan PSB, but inconsistencies are observed with carbamazepine, divalproex, everolimus, levothyroxine, liothyronine, sirolimus, and theophylline. It is important to note that FDA continues to evaluate whether additional drug products, including those identified in literature or by other regulatory agencies, meet the general characteristics of an NTI drug. However, at the current moment, there appears to be a lack of harmonization across regulatory agencies with regard to the terms, definitions, and published lists of drugs considered as NTI or described with a related term.

CONCLUSIONS AND FUTURE DIRECTIONS

In summary, following advisory committee recommendations, FDA leveraged the diverse expertise of the NTI Drug Working Group to provide a definition for NTI drugs, promote the consistent use of this term in its regulatory documents, and recommend tighter quality and BE standards to ensure the therapeutic

15326535, 2025, 1, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3460 by Us Fda, Wiley Online Library on [13/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 5 Comparison of drugs referred to as NTI drugs or related terminology across regulatory agencies[a]

Drug Name/Class	FDA[31]	EMA[15]	Health Canada[13]	Japan PSB[16]
Acenocoumarol		NTID		
Aprindine				NTRD
Carbamazepine	NTID			
Carmazepine				NTRD
Clindamycin				NTRD
Clonazepam				NTRD
Clonidine				NTRD
Colchicine		NTID		
Cyclosporine	NTID		CDD	NTRD
Digitoxin				NTRD
Digoxin	NTID		CDD	NTRD
Disopyramide				NTRD
Divalproex	NTID			
Ethinyl Estradiol				NTRD
Ethosuximide				NTRD
Everolimus	NTID	NTID		
Flecainide			CDD	
Glybuzole				NTRD
Guanethidine				NTRD
Isoprenaline				NTRD
Levothyroxine/Levothyroxine Sodium	NTID	CCD		
Liothyronine/Liothyronine Sodium	NTID			
Lithium/Lithium Carbonate	NTID		CDD	NTRD
Methotrexate				NTRD
Phenobarbital				NTRD
Phenytoin/Phenytoin Sodium	NTID		CCD	NTRD
Prazosin				NTRD
Primidone				NTRD
Procainamide				NTRD
Quinidine				NTRD
Sirolimus	NTID	NTID	CDD	
Sulfonylurea antidiabetic drug compounds[b]				NTRD
Tacrolimus	NTID	NTID	CDD	NTRD
Theophylline	NTID		CDD	
Theophylline compounds[c]				NTRD
Valproic acid	NTID			NTRD
Warfarin/Warfarin Sodium	NTID		CDD	NTRD
Zonisamide				NTRD

CDD, critical dose drug; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; NTID, narrow therapeutic index drug; NTRD, narrow therapeutic range drug; PSB, Pharmaceutical Safety Bureau (formerly known as Pharmaceutical Food and Safety Bureau[12]). [a]Here, the term "drug" may refer to an active ingredient, or a drug product containing an active ingredient, referred to as an NTI drug or related terminology. [b]Acetohexamide, glibenclamide, gliclazide, glyclopyramide, tolazamide, and tolbutamide. [c]Aminophylline, choline theophylline, diprophylline, proxyphylline, and theophylline.

equivalence of generic NTI drugs to their respective RLDs. In addition, FDA has made efforts to enhance public confidence in the quality of NTI drugs and therapeutic equivalence of generic drugs through public workshops, research, and post-marketing surveillance. This report summarizes the process at FDA to evaluate candidate NTI drugs, provides the current list of drug products for which FDA has published product-specific draft guidance identifying that they demonstrate the characteristics of NTI drugs, and outlines FDA's current BE recommendations for NTI drugs. Further harmonization of NTI drug classification and BE approaches is warranted among global regulatory agencies.

15326535, 2025, 1, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3460 by Us Fda, Wiley Online Library on [13/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

ACKNOWLEDGMENTS
The authors would like to thank Zhen Zhang (OGD/OB), Ke Ren (OGD/OB), Li Xia (OGD/OB), Fairouz Makhlouf (OTS/OB), and Stell Grosser (OTS/OB) at the FDA for their comments on the manuscript and contributions to the NTI Drug Working Group.

FUNDING
No funding was received for this work.

CONFLICT OF INTEREST
The authors declared no competing interests for this work.

DISCLAIMER
The opinions expressed herein are those of the authors and should not be interpreted as the position of the U.S. Food and Drug Administration.

© 2024 The Author(s). *Clinical Pharmacology & Therapeutics*
© 2024 American Society for Clinical Pharmacology and Therapeutics.

1. Burns, M. Management of narrow therapeutic index drugs. *J Thromb Thrombolysis* **7**, 137–143 (1999).
2. Tamargo, J., Le Heuzey, J.Y. & Mabo, P. Narrow therapeutic index drugs: a clinical pharmacological consideration to flecainide. *Eur J Clin Pharmacol* **71**, 549–567 (2015).
3. Benet, L.Z. Relevance of pharmacokinetics in narrow therapeutic index drugs. *Transplant Proc* **31**, 1642; discussion 1675–1684–1644 (1999).
4. Yu, L.X. *et al*. Novel bioequivalence approach for narrow therapeutic index drugs. *Clin Pharmacol Ther* **97**, 286–291 (2015).
5. Jiang, W. & Yu, L.X. Bioequivalence for narrow therapeutic index drugs. In *FDA Bioequivalence Standards* (eds. Yu, L. & Li, B.V.) 191–216 (Springer, New York, NY, 2014).
6. Gozzo, L., Caraci, F. & Drago, F. Bioequivalence, drugs with narrow therapeutic index and the phenomenon of biocreep: a critical analysis of the system for generic substitution. *Healthcare* **10** (2022).
7. Caffrey, A.R. & Borrelli, E.P. The art and science of drug titration. *Ther Adv Drug Saf* **11**, 2042098620958910 (2020).
8. Currie, G.M. Pharmacology, part 1: introduction to pharmacology and pharmacodynamics. *J Nucl Med Technol* **46**, 81–86 (2018).
9. Tyson, R.J. *et al*. Precision dosing priority criteria: drug, disease, and patient population variables. *Front Pharmacol* **11**, 420 (2020).
10. Habet, S. Narrow therapeutic index drugs: clinical pharmacology perspective. *J Pharm Pharmacol* **73**, 1285–1291 (2021).
11. Jiang, W. *et al*. A bioequivalence approach for generic narrow therapeutic index drugs: evaluation of the reference-scaled approach and variability comparison criterion. *AAPS J* **17**, 891–901 (2015).
12. Update on Japan Regulatory Agency, Content current as of November 27, 2023 <https://www.fda.gov/international-programs/international-arrangements/update-japan-regulatory-agency> (2023). Cited January 5, 2024.
13. Guidance Document – Comparative Bioavailability Standards: Formulations Used for Systemic Effects <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/bioavailability-bioequivalence/comparative-bioavailability-standards-formulations-used-systemic-effects.html> (2012). Cited January 5, 2024. Accessed September 1, 2018.
14. Guideline on the Investigation of Bioequivalence (Rev. 1), Committee for Medicinal Products for Human Use (CHMP), First published: January 1, 2010, Last updated: March 10, 2010, Legal effective date: August 1, 2010, Reference Number: CPMP/EWP/QWP/1401/98 Rev. 1. 2010 August 1, 2010 <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf>.
15. Product-specific bioequivalence guidance <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/product-specific-bioequivalence-guidance>. Cited October 19, 2023.
16. Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms, English translation of Attachment 2 of Division-Notification 0229 No. 10 of the Pharmaceutical and Food Safety Bureau <https://www.nihs.go.jp/drug/be-guide(e)/strength/GL-E_120229_ganryo.pdf> (2012). Accessed February 29, 2012.
17. Code of Federal Regulations (CFR), Title 21, Subchapter D, Part 320, Subpart B, Section 320.33: Criteria and evidence to assess actual or potential bioequivalence problems [21CFR320.33] <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-320>. Accessed August 25, 2023.
18. SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation, Guidance for Industry <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/supac-ir-immediate-release-solid-oral-dosage-forms-scale-and-post-approval-changes-chemistry> (1995).
19. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, Guidance for Industry, Draft Guidance, August 1999 <https://www.regulations.gov/document/FDA-1999-D-4088-0002> (1999).
20. Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling, Guidance for Industry <https://downloads.regulations.gov/FDA-2006-D-0036-0002/attachment_1.pdf> (2006).
21. Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling, Guidance for Industry <https://downloads.regulations.gov/FDA-2006-D-0036-0032/content.pdf> (2012).
22. Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee <https://wayback.archive-it.org/7993/20170403224116/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm201700.htm> (2012).
23. Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee <https://wayback.archive-it.org/7993/20170403224114/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm240583.htm> (2011).
24. Citizen Petition to FDA, Docket: FDA-2020-P-1247, Final Response Letter from FDA CDER to Belcher Pharmaceuticals, LLC. (FDA-2020-P-1247-0006) <https://www.regulations.gov/document/FDA-2020-P-1247-0006> (2023).
25. Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA, Guidance for Industry <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioequivalence-studies-pharmacokinetic-endpoints-drugs-submitted-under-abbreviated-new-drug> (2021).
26. Generic Competition and Drug Prices, Content current as of September 12, 2022 <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/generic-competition-and-drug-prices> (2022).
27. FDA Drug Competition Action Plan: Helps remove barriers to generic drug development and market entry so that consumers can get access to needed medicines, Content current as of June 9, 2023 <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/fda-drug-competition-action-plan> (2023).
28. FDA Orange Book Preface, Approved Drug Products with Therapeutic Equivalence Evaluations, Preface to 43rd Edition, Content current as of January 24, 2023 <https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface> (2023).
29. Rome, B.N., Sarpatwari, A. & Kesselheim, A.S. State Laws and Generic substitution in the year after new Generic competition. *Value Health* **25**, 1736–1742 (2022).
30. Code of Federal Regulations (CFR), Title 21, Subchapter D, Part 314, Subpart A, Section 314.3(b): Definitions [21CFR314.3(b)] <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314/subpart-A/section-314.3> (2023).

15326535, 2025, 1, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3460 by Us Fda, Wiley Online Library on [13/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

31. Product-Specific Guidances for Generic Drug Development, Content current as of November 21, 2022 <https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development> (2022).
32. Draft product-specific guidance on warfarin sodium oral tablet, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg, referencing NDA 009218, Recommended Dec 2012 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/Warfarin_Sodium_tab_09218_RC12-12.pdf> (2012).
33. Statistical Approaches to Establishing Bioequivalence <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-approaches-establishing-bioequivalence-0> (2022).
34. FDA Q&A: Generic Versions of Narrow Therapeutic Index Drugs National Survey of Pharmacists' Substitution Beliefs and Practices <https://globalforum.diaglobal.org/issue/july-2019/fda-qa-generic-versions-of-narrow-therapeutic-index-drugs-national-survey-of-pharmacists-substitution-beliefs-and-practices/> (2019).
35. FDA Webinar: "FDA Drug Topics: Understanding Generic Narrow Therapeutic Index Drugs", FDA's Division of Drug Information in the Center for Drug Evaluation and Research (CDER), Presented by Wenlei Jiang, Ph.D. on November 1, 2022, content current as of January 6, 2023 <https://www.fda.gov/about-fda/fda-pharmacy-student-experiential-program/understanding-generic-narrow-therapeutic-index-drugs ; https://www.fda.gov/media/162779/download> (2022).
36. Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations, Guidance for Industry <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-studies-submitted-ndas-or-inds-general-considerations> (2022).
37. Citizen Petition to FDA, Docket: FDA-2020-P-1247, Citizen Petition from Belcher Pharmaceuticals, LLC, Submitted on April 3, 2020 <https://www.regulations.gov/document/FDA-2020-P-1247-0001> (2020).
38. Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances, Guidance for Industry (2018).
39. Product-Specific Guidance Meetings Between FDA and ANDA Applicants Under GDUFA Guidance for Industry <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-specific-guidance-meetings-between-fda-and-anda-applicants-under-gdufa> (2023).
40. Code of Federal Regulations (CFR), Title 21, Subchapter D, Part 320, Subpart B, Section 320.24: Types of evidence to measure bioavailability or establish bioequivalence [21CFR320.24] <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-320/subpart-B/section-320.24> (2023).
41. Citizen Petition to FDA, Docket: FDA-2019-P-3545, Response Letter from FDA CDER to Axinn, Veltrop & Harkrider LLP (FDA-2019-P-3545-0008), Posted December 19, 2019 <https://www.regulations.gov/document/FDA-2019-P-3545-0008> (2019).
42. Citizen Petition to FDA, Docket: FDA-2015-P-4566, Final Response from FDA CDER to Buchanan Ingersoll & Rooney PC (FDA-2015-P-4566-0005), Posted August 30, 2017 <https://www.regulations.gov/document/FDA-2015-P-4566-0005> (2017).
43. FY2015 Regulatory Science Research Report: Narrow Therapeutic Index Drugs, Content current as of May 9, 2017 <https://www.fda.gov/industry/generic-drug-user-fee-amendments/fy2015-regulatory-science-research-report-narrow-therapeutic-index-drugs> (2015).
44. FY2016 Regulatory Science Report: Postmarket: Patient Substitution Studies, Content current as of March 28, 2017 <https://www.fda.gov/industry/generic-drug-user-fee-amendments/fy2016-regulatory-science-report-postmarket-patient-substitution-studies> (2016).
45. FY2022 GDUFA Science and Research Report, Patient Substitution of Generic Drugs <https://www.fda.gov/media/164843/download> (2022).
46. Brito, J.P. *et al*. Comparative effectiveness of generic vs brand-name levothyroxine in achieving Normal thyrotropin levels. *JAMA Netw Open* **3**, e2017645 (2020).
47. Desai, R.J. *et al*. Comparative outcomes of treatment initiation with brand vs. generic warfarin in older patients. *Clin Pharmacol Ther* **107**, 1334–1342 (2020).
48. Real-world Evidence from a Narrow Therapeutic Index Product (Levothyroxine) Reflects the Therapeutic Equivalence of Generic Drug Products, Content current as of November 19, 2020 <https://www.fda.gov/drugs/news-events-human-drugs/real-world-evidence-narrow-therapeutic-index-product-levothyroxine-reflects-therapeutic-equivalence> (2020).
49. Questions and Answers on FDA's Adverse Event Reporting System (FAERS), Content current as of June 4, 2018 <https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers> (2018).
50. FDA's Sentinel Initiative, Content current as of February 2, 2023 <https://www.fda.gov/safety/fdas-sentinel-initiative> (2023).
51. Science & Research, Office of Generic Drugs (OGD) <https://www.fda.gov/drugs/generic-drugs/science-research>.
52. Citizen Petition to FDA, Docket: FDA-2011-P-0654, Request to Disapprove Abbreviated New Drug Application 78–868 Filed by Apotex, Inc. for Generic Tizanidine Hydrochloride Capsules-CLOSED <https://www.regulations.gov/docket/FDA-2011-P-0654> (2011).
53. Citizen Petition to FDA, Docket: FDA-2014-P-2193, Requests that the FDA take the actions with respect to the bioequivalence criteria required of abbreviated new drug applications ("AND As") for dalfampridine filed under section 505(j) of the FDCA, citing Acorda's product Ampyra as the reference listed drug ("RLD") <https://www.regulations.gov/docket/FDA-2014-P-2193> (2014).
54. Generic Drug User Fee Amendments III (GDUFA III), Reauthorization Performance Goals and Program Enhancements, Fiscal Years 2023–2027 <https://www.fda.gov/media/153631/download>.
55. M9 Biopharmaceutics Classification System-Based Biowaivers, Guidance for Industry <https://www.fda.gov/media/148472/download> (2021).
56. Draft product-specific guidance for clonazepam oral tablet, referencing NDA 017533, Finalized August 2017 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/Clonazepam_Oral%20Tablet_RLD%2017533_Final%2008-17.pdf> (2017).
57. M13A bioequivalence for immediate-release solid oral dosage forms, January 2023 <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m13a-bioequivalence-immediate-release-solid-oral-dosage-forms> (2024). Cited August 8, 2024.
58. Draft product-specific guidance for theophylline for extended-release tablets, 400 mg and 600 mg, referencing ANDA 040560, Recommended Feb 2010; revised Aug 2020 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_085328-TabER-600MG.pdf> (2020).
59. Draft product-specific guidance for theophylline for extended-release capsules, 100 mg, 200 mg, 300 mg, and 400 mg referencing ANDA 081034, Recommended Feb 2010; revised Aug 2020 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_087942.pdf> (2020).
60. Draft product-specific guidance for theophylline for extended-release tablets, 100 mg, 200 mg, 300 mg, and 450 mg referencing ANDA 090430, ANDA 086998, or ANDA 085328, Recommended Feb 2010; Withdrawn Aug 2020; Revised May 2022 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_085328.pdf> (2022).
61. Draft product-specific guidance for cyclosporin oral capsules, 25 mg, 50 mg, and 100 mg, referencing NDA 050625, Recommended Mar 2015; Revised Apr 2016 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/Cyclosporine_Oral%20capsule_RLD%20050625_RV04-16.pdf> (2016).
62. Draft product-specific guidance for cyclosporin oral capsules, 25 mg, and 100 mg, referencing NDA 050715, Recommended Mar 2015; Revised Apr 2016 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/Cyclosporine_Oral%20capsule_RLD%20050715_RV04-16.pdf> (2016).
63. Draft product-specific guidance for cyclosporin ophthalmic emulsion, 0.1%, referencing NDA 214965, Recommended Aug 2022 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_214965.pdf> (2022).

15326535, 2025, 1, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3460 by Us Fda, Wiley Online Library on [13/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

64. Draft product-specific guidance for cyclosporin ophthalmic emulsion, 0.05%, referencing NDA 050790, Recommended Jun 2013; Revised Feb 2016; Oct 2016 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/Cyclosporine_ophthalmic%20emulsion_RLD%20050790_RV09-16.pdf> (2016).
65. Draft product-specific guidance for cyclosporin ophthalmic solution/drops, 0.09%, referencing NDA 210913, Recommended May 2019 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/Cyclosporine%20ophthalmic%20solution%200.09%20NDA%20210913%20PSG%20Page%20RC%20May%202019.pdf> (2019).
66. Product labeling for AFINITOR® (everolimus) oral tablets and AFINITOR DISPERZ® (everolimus tablets for oral suspension), Updated April 2021 <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2150f73a-179b-4afc-b8ce-67c85cc72f04> (2021).
67. Draft product-specific guidance for everolimus oral tablet for suspension, 2 mg, 3 mg, and 5 mg, referencing NDA 203985, Recommended Oct 2017 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/Everolimus_oral%20tablet%20for%20suspension_NDA%20203985_RC08-17.pdf> (2017).
68. Draft product-specific guidance for everolimus oral tablet, 2.5 mg, 5 mg, 7.5 mg, and 10 mg, referencing NDA 022334, Recommended Sept 2015; Revised Mar 2017, Nov 2018 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/Everolimus_draft_Oral%20tab_RLD%2022334_RC11-18.pdf> (2018).
69. Product labeling for ZORTRESS® (everolimus) oral tablets, Updated May 16, 2022 <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e082a024-7850-400b-a5c2-2a140612562a> (2022).
70. Draft product-specific guidance for everolimus oral tablet, 0.25 mg, 0.5 mg, 0.75 mg, and 1 mg, referencing NDA 021560, Recommended Jun 2016; Revised Jun 2020 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021560.pdf> (2020).
71. Draft product-specific guidance for dabigatran etexilate mesylate oral capsules, 75 mg, 110 mg, 150 mg, referencing NDA 022512, Recommended Jun 2012; Revised Sept 2015, Jul 2017 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/Dabigatran%20etexilate%20mesylate_oral%20capsule_NDA%20022512_RV05-17.pdf> (2017).
72. Draft product-specific guidance for rivaroxaban oral tablets, 2.5 mg, 10 mg, 15 mg, and 20 mg, referencing NDA 022406, Recommended Sep 2015; Revised Aug 2020 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022406.pdf> (2020).
73. Draft product-specific guidance for edoxaban tosylate oral tablets, 15 mg, 30 mg and 60 mg, referencing NDA 206316, Recommended May 2017; Revised Mar 2020 <https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_206316.pdf> (2020).
74. Acenocoumarol, tablet, 1 mg and 4 mg product-specific bioequivalence guidance – First version, First published: September 13, 2021, Last updated: September 22, 2021, Reference Number: EMA/CHMP/512475/2020 Corr., Legal effective date: April 1, 2022 <https://www.ema.europa.eu/en/documents/scientific-guideline/acenocoumarol-tablet-1-mg-and-4-mg-product-specific-bioequivalence-guidance-first-version_en.pdf>. Cited January 5, 2024 (2022).
75. Colchicine tablet 0.5 mg and 1 mg product-specific bioequivalence guidance, First published: October 15, 2019, Reference Number: EMA/CHMP/35552/2019, Legal effective date: April 1, 2020. 2020 August 22, 2024 <https://www.ema.europa.eu/en/documents/scientific-guideline/colchicine-tablet-05-mg-and-1-mg-product-specific-bioequivalence-guidance_en.pdf> (2020).
76. Everolimus tablets 0.25, 0.5, 0.75 and 1 mg; 2.5, 5 and 10 mg, dispersible tablets 0.1 and 0.25 mg; 2, 3 and 5 mg product-specific bioequivalence guidance (draft), Draft: consultation closed, First published: May 2, 2016, Last updated: May 2, 2016, Consultation dates: May 2, 2016 to July 31, 2016, Reference Number: EMA/CHMP/154772/2016 <https://www.ema.europa.eu/en/documents/scientific-guideline/draft-everolimus-tablets-025-05-075-and-1mg-25-5-and-10mg-dispersible-tablets-01-and-025mg-2-3-and-5mg-product-specific-bioequivalence-guidance_en.pdf> (2016). Accessed August 22, 2024.
77. Sirolimus coated tablets 0.5, 1 and 2 mg, oral solution 1 mg/ml product-specific bioequivalence guidance, First published: May 25, 2016, Last updated: May 25, 2016, Reference Number: EMA/CHMP/315231/2014, Legal effective date: December 1, 2015 <https://www.ema.europa.eu/en/documents/scientific-guideline/sirolimus-coated-tablets-05-1-and-2-mg-oral-solution-1-mgml-product-specific-bioequivalence-guidance_en.pdf> (2016). Accessed August 22, 2024.
78. Tacrolimus granules for oral suspension 0.2 and 1 mg product-specific bioequivalence guidance, First published: May 25, 2016, Last updated: November 1, 2016, Reference Number: EMA/CHMP/159744/2016, Legal effective date: November 1, 2016 <https://www.ema.europa.eu/en/documents/scientific-guideline/tacrolimus-granules-oral-suspension-02-and-1-mg-product-specific-bioequivalence-guidance_en.pdf> (2016). Accessed August 22, 2024.
79. Levothyroxine tablets 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 100 mcg and 200 mcg (and additional strengths within the range) product-specific bioequivalence guidance, First published: December 16, 2020, Reference Number: EMA/CHMP/176098/2020 <https://www.ema.europa.eu/en/documents/scientific-guideline/levothyroxine-tablets-125-mcg-25-mcg-50-mcg-75-mcg-100-mcg-and-200-mcg-and-additional-strengths-within-range-product-specific-bioequivalence-guidance_en.pdf> (2020). Accessed January 5, 2024.
80. Product labeling for theophylline (anhydrous) extended-release tablet, 400 and 600 mg <https://dailymed.nlm.nih.gov/dailymed/downloadpdffile.cfm?setId=aa80b9f4-8a5d-3e14-e053-2a95a90a8aab> (2021).
81. Bredon, J.W., Bootman, J.L., Jones, W.N., McGhan, W.F., Perrier, D.G. & Campbell, S.C. Theophylline serum concentrations in ambulatory patients with chronic obstructive pulmonary disease. *Ther Drug Monit* **7**, 168–173 (1985).
82. McKay, S.E., Howie, C.A., Thomson, A.H., Whiting, B. & Addis, G.J. Value of theophylline treatment in patients handicapped by chronic obstructive lung disease. *Thorax* **48**, 227–232 (1993).
83. Hendeles, L., Bighley, L., Richardson, R.H., Hepler, C.D. & Carmichael, J. Frequent toxicity from IV aminophylline infusions in critically ill patients. 1977. *Ann Pharmacother* **40**, 1417–1423 (2006).
84. Jenne, J.W., Wyze, M.S., Rood, F.S. & MacDonald, F.M. Pharmacokinetics of theophylline. Application to adjustment of the clinical dose of aminophylline. *Clin Pharmacol Ther* **13**, 349–360 (1972).
85. Sublett, J.L., Pollard, S.J., Kadlec, G.J. & Karibo, J.M. Non-compliance in asthmatic children: a study of theophylline levels in a pediatric emergency room population. *Ann Allergy* **43**, 95–97 (1979).
86. Tonnesen, J. Serum theophylline during acute asthmatic attacks. *Int Arch Allergy Appl Immunol* **73**, 280–282 (1984).
87. Barnes, P.J. Theophylline. *Am J Respir Crit Care Med* **188**, 901–906 (2013).
88. Hendeles, L. & Weinberger, M. Theophylline A "state of the art" review. *Pharmacotherapy* **3**, 2–44 (1983).
89. Mungall, D. *et al*. Individualizing theophylline therapy: the impact of clinical pharmacokinetics on patient outcomes. *Ther Drug Monit* **5**, 95–101 (1983).
90. Jacobs, M.H., Senior, R.M. & Kessler, G. Clinical experience with theophylline. Relationships between dosage, serum concentration, and toxicity. *JAMA* **235**, 1983–1986 (1976).
91. Baker, M.D. Theophylline toxicity in children. *J Pediatr* **109**, 538–542 (1986).
92. Emerman, C.L., Devlin, C. & Connors, A.F. Risk of toxicity in patients with elevated theophylline levels. *Ann Emerg Med* **19**, 643–648 (1990).
93. Gaudreault, P., Wason, S. & Lovejoy, F.H. Jr. Acute pediatric theophylline overdose: a summary of 28 cases. *J Pediatr* **102**, 474–476 (1983).

15326535, 2025, 1, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3460 by Us Fda, Wiley Online Library on [13/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

94. Burkle, W.S. & Gwizdala, C.J. Evaluation of "toxic" serum theophylline concentrations. *Am J Hosp Pharm* **38**, 1164–1166 (1981).
95. Zwillich, C.W., Sutton, F.D., Neff, T.A., Cohn, W.M., Matthay, R.A. & Weinberger, M.M. Theophylline-induced seizures in adults. Correlation with serum concentrations. *Ann Intern Med* **82**, 784–787 (1975).
96. Ried, L.D., Horn, J.R. & McKenna, D.A. Therapeutic drug monitoring reduces toxic drug reactions: a meta-analysis. *Ther Drug Monit* **12**, 72–78 (1990).

15326535, 2025, 1, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3460 by Us Fda, Wiley Online Library on [13/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License